Citation:

De Wals P, Tairou F, Van Allen MI, Lowry RB, Evans JA, Van den Hof MC, Crowley M, Uh SH, Zimmer P, Sibbald B, Fernandez B, Lee NS, Niyonsenga T. Spina bifida before and after folic acid fortification in Canada. *Birth Defects Res A Clin Mol Teratol.* 2008; 82 (9): 622-626.

PubMed ID: 18655127

Study Design:

Retrospective cohort study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To test the hypotheses:

- That in the pre-fortification period, upper defects would be more frequent in the eastern provinces of Canada where NTD prevalence was historically higher than in the western provinces
- That the effect of fortification would be greater for upper than for lower spinal defects.

Inclusion Criteria:

Women residents in seven Canadian provinces from 1993 to 2002 who had:

- Live births
- Stillbirths
- Termination of pregnancies because of fetal anomaly.

Details described in a previous publication.

Exclusion Criteria:

- Spina bifida associated with anencephaly
- Iniencephaly cases
- Cases of occult spinal dysraphism (namely spina bifida occulta, thickened filium terminale, diastematomyelia, caudal regression syndrome, intradural lipoma, lipomeningomyelocele, split notocord and other forms of myelodysplasia).

Description of Study Protocol:

Recruitment

- The study included live births, stillbirths and termination of pregnancies because of fetal anomaly to women residents in seven Canadian provinces, from 1993 to 2002
- Figures were provided by provincial statistics offices and included 1,913,114 live- and stillbirths.

Design

Retrospective cohort study.

Statistical Analysis

- *Prevalence rates:* Calculated as the sum of spina bifida cases in live births, stillbirths and induced abortions, divided by total live- and stillbirths
- *Theoretical birth date:* In order to prevent any classification bias in calculating birth prevalence rates, was calculated for each NTD case assuming a gestation of 40 weeks (date of birth/abortion; gestation length in weeks + 40 weeks) since a large proportion of NTD-affected pregnancies were terminated
- *Provinces:* Grouped into an eastern (Newfoundland and Labrador, Nova Scotia, and Prince Edward Island), a central (Quebec and Manitoba) and a western region (Alberta and British Columbia)
- *The chi-square test (for difference in proportions) and the Cochrane-Armitage test (for linear trend in proportions):* Performed at the statistical significance leve of 5% (two-sided tests)
- *Multivariate logistic model:* Used to analyze variation in the upper-to-lower spina bifida case ratio, taking into account the fortification period (three categories), the region (three categories) and the type of birth (three categories)
- SAS 8.1 software (SAS Institute, Cary, NC) was used.

Data Collection Summary:

Timing of Measurements

Ascertainment of NTD cases from 1993 to 2002.

Dependent Variables

- *NTD cases (through multiple sources):*
    - *Medical records (including clinical descriptions, pathology reports and radiology examinations) of suspected NTD cases:* Reviewed by experienced medical archivists or

specially trained research persons. Between 95% and 100% of records could be found
    - *All medical diagnoses:* Reviewed by one of the authors
- *Spina bifida cases:* Classified according to the upper limit of the spinal defect as recorded in medical charts. Cases were further grouped into upper (cranial, cervical and thoracic) and lower (lumbar and sacral) defects.

Independent Variables

Fortification period:

- *All births ending before September 30, 1997:* Belonging to the pre-fortification period (N=970,191)
- *Those between October 1, 1997 and March 31, 2000*: Belonging to a partial fortification period (N=455,889)
- *Those after this date:* Occurring during the full fortification period (N=487,034). This categorization was based on results of biochemical tests in a large Ontario laboratory, which showed that concentrations of red blood cell folate in the population started to increase in April, 1997 and reached a plateau in February, 1999. Given this finding and assuming that there is no beneficial effect of folic acid after the end of the first trimester, the paper made the above grouping for fortification period.

Control Variables

- *The region:* Provinces, grouped into an eastern (Newfoundland and Labrador, Nova Scotia, and Prince Edward Island), a central (Quebec and Manitoba) and a western region (Alberta and British Columbia)
- *The type of birth:* Live birth, stillbirth or induced abortion
- Gender.

Description of Actual Data Sample:

- *Initial N:* Two million live births, stillbirths and terminations of pregnancies because of fetal anomalies between 1993 and 2002
- *Attrition (final N):* 1,913,114 live- and stillbirths and a total of 1,286 spina bifida cases (51% live births, 3% stillbirths, and 46% terminations)
- *Location:* Seven Canadian provinces (Newfoundland and Labrador, Nova Scotia, Prince Edward Island, Quebec and Manitoba, Alberta and British Columbia).

Summary of Results:

Table 1. Distribution (and Percentage*) of Spina Bifida Cases According to the Upper Limit of the NTD, and Other Characteristics, in Seven Canadian Provinces, 1993 to 2002

	Upper Limit of Defect						
	Cranial	Cervical	Thoracic	Lumbar	Sacral	Unknown	Total
All cases	12 (1.4)	28 (3.3)	183 (21.9)	486 (58.1)	127 (15.2)	450	1, 286
Pregnancy outcome							

Live birth	3 (0.7)	17 (3.7)	107 (23.6)	252 (55.5)	75 (16.5)	202	656
Stillbirth	0 (0.0)	1 (4.5)	8 (36.4)	8 (36.4)	5 (22.7)	13	35
Induced abortion	9 (2.5)	10 (2.8)	68 (18.9)	226 (62.8)	47 (13.1)	235	595
Province							
Newfoundland & Labrador	0 (0.0)	1 (1.2)	37 (45.7)	41 (50.6)	2 (2.5)	1	82
Nova Scotia & Prince Edward Island	3 (3.0)	2 (2.0)	39 (39.0)	50 (50.0)	6 (6.0)	8	108
Quebec	0 (0.0)	13 (5.6)	21 (9.0)	141 (60.5)	58 (24.9)	404	637
Manitoba	5 (5.3)	4 (4.3)	19 (20.2)	56 (59.6)	10 (10.6)	2	96
Alberta	4 (2.8)	6 (4.2)	38 (26.4)	78 (54.2)	18 (12.5)	12	156
British Columbia	0 (0.0)	2 (1.1)	29 (15.8)	120 (65.2)	33 (17.9)	23	207
Fortification period							
Pre-†	7 (1.3)	21 (3.9)	145 (26.7)	304 (56.0)	66 (12.2)	287	830
Partial‡	2 (1.2)	6 (3.5)	26 (15.3)	101 (59.4)	35 (20.6)	90	260
Full §	3 (2.4)	1 (0.8)	12 (9.8)	81 (65.9)	26 (21.1)	73	196
Gender							
Male	8 (2.1)	14 (3.6)	81 (20.9)	231 (59.7)	53 (13.7)	187	574
Female	4 (1.0)	12 (2.9)	96 (22.9)	237 (56.6)	70 (16.7)	222	641
Indeterminate	0 (0.0)	0 (0.0)	1 (33.3)	1 (58.3)	0 (8.3)	0	2
Unknown	0 (1.5)	0 (3.2)	4 (22.2)	7 (58.0)	1 (15.1)	57	69

* Expressed as the percentage of cases for which the information on the site is known. † Up to September 30, 1997. ‡ October 1, 1997 to March 31, 2000. § April 1, 2000 or later.

Table 2. Site of Defect in Spina Bifida (SB) Cases According to Region and Fortification Period, in Seven Canadian Provinces, 1993 to 2002

	Fortification Period		
Region and Site	**Pre- (Up to September 30, 1997)**	**Partial (October 1, 1997 to March 31, 2000)**	**Full (April 1, 2000 or Later)**
Eastern provinces*			
Upper SB	68	11	3
Lower SB	74	12	13
Site unknown	8	0	1
All SB	150	23	17
Births	89,136	40,662	41,551
Central provinces†			
Upper SB	47	10	5
Lower SB	161	57	49
Site unknown	257	82	68
All SB	465	149	122
Births	474,408	215,094	229,751
Western provinces‡			
Upper SB	58	13	8
Lower SB	135	67	45
Site unknown	22	7	4
All SB	215	87	57

Births	406,647	200,133	215,732

* Newfoundland & Labrador, Nova Scotia, Prince-Edward-Island.

† Quebec, Manitoba.

‡ Alberta, British Columbia.

Other Findings

- The proportion of unknown information on the upper limit of defect was slightly lower for live birth than for stillbirth cases and induced abortions (P<0.01)
- There was no significant difference in the proportion of unknown site according to the fortification period
- An upper defect was present in 26.7% of spina bifida cases
- The overall proportion of spina bifida-affected pregnancies ending in voluntary termination was 46%, and this proportion was 39.0% for upper spina bifida and 44.5% for lower spina bifida (P=0.15)
- The proportion of upper defects was much higher in the eastern provinces than in the central and western provinces (P<0.001)
- The proportion of upper defects was higher during the pre-fortification period than that during the partial fortification period, and during the full fortification period (P for linear trend was less than 0.001)
- Excluding cases of unknown or indeterminate gender, the female proportion was 52.8% for all spina bifida cases, and was not statistically different for upper (52.1%) and for lower defects (51.1%)
- The overall prevalence rate of spina bifida decreased from 0.86 out of 1,000 during the pre-fortification period to 0.57out of 1,000 during the partial fortification period, and to 0.40 out of 1,000 during the full fortification period (P for linear trend was less than 0.0001)
- Before fortification was implemented, there was a statistically significant geographical trend in the prevalence of spina bifida (P for linear trend less than 0.0001), with a rate of 1.68 out of 1,000 in the eastern region, 0.98 out of 1,000 in the central region, and 0.53 out of 1,000 in the western region
- After fortification was fully implemented, there was no linear gradient, although the rate in the western region (0.26 out of 1,000) remained lower than that in the central (0.53 out of 1,000) and eastern (0.41 out of 1,000) regions (P<0.0001)
- Before fortification was implemented, the proportion of upper defects was 47.9% in the eastern region, 22.5% in the central region, and 30.1% in the western region (P<0.0001)
- When fortification fully implemented, the proportion of upper defects decreased in all regions and geographical differences disappeared, the proportion of upper defects being, respectively, 18.8%, 9.3%, and 15.1% in the eastern, central, and western regions respectively (P=0.51)
- In the multivariate analysis, the effect of fortification in reducing the proportion of upper defects remained while controlling for the region and for the type of birth (OR 0.56; 95% CI: 0.34 to 0.91; P=0.02 for the partial fortification vs. pre-fortification period; and OR 0.31; 95% CI: 0.16 to 0.60; P<0.001 for the full fortification vs. pre-fortification period)
- A similar result was obtained when the province of Quebec was excluded from the analysis (OR 0.61; 95%CI: 0.40 to 0.95; P=0.03 for the partial fortification vs. pre-fortification period; OR 0.35; 95%CI: 0.19 to 0.62; P<0.001 for the full fortification vs. pre-fortification period)

- Gender was not included in the final models, since it was not associated with variation in outcome.

Author Conclusion:

Results confirmed the etiologic heterogeneity of spina bifida and the more pronounced effect of folic acid in decreasing the risk of the more severe clinical presentations.

Reviewer Comments:

- *Information on the upper limit of the defect was not available for 450 cases (35% of the total). In Quebec the information was not available for 63.4% of cases*
- *Cases of spina bifida associated with anencephaly were excluded*
- *In Quebec the upper site of the spinal defect was identified as only 37%, lower than other provinces, which was an indicator of low quality of hospital records in Quebec*
- *This study did not attempt to distinguish spina bifida cases diagnosed by clinical examination or on the basis of ultrasound from those confirmed by an X-ray examination providing details on the extent of vertebral defects*
- *In this study, some degree of misclassification of upper and lower spina bifida cases cannot excluded, but it should not be believed that such misclassification bias would have been of high magnitude and markedly different according to fortification periods.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes

1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	No
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	???
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	???
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A

5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	???
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	N/A
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes

7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	???
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes